Fig.1

Human A4 Receptor

TTGAGCCGGCAGACTGCGAAAAGTAGCTGGAGCCGGACAGAGAACCTGTTGCTGCAGACGGGCTTGGTGCGATTCTGGTTCCTGCGCCGGAGAGGTTCATC — 120

ATGAATGAGAAATGGGACACAAAACTCTTCAGAAAACTGCATCCCATCTGGAATGCCAATGACACAAAGCATCATCTACTCTGACATATTAATATTACTTAC — 240
M N E K W D T N S S E N W H P I W N V N D T K H H L Y S D I N I T Y V N Y Y L H — 40

CAGCCTCAAGTGGCCAGCAATCTTCATTATTTCCTACTTTCTGCTCTTTGTGCATGATGGGAAATACTGTGTTTGCTTATTGTAATGAGGAACAAACATATGCCACACAGTCACT — 360
Q P Q V A A I F I I S Y F L I F F L C M M G N T V V C F I V M R N K H M H T V T — 80

AATCTCTTCATCTTAAACCTGGCCATAAGTGATTTACTAGTTGGCATATTCTGCATGCCTATAACACTGCTGGACAATATTATAGCCATTGGAAACACGATGTGCAAGATC — 480
N L F I L N L A I S D L L V G I F C M P I T L L D N I I A G W P F G N T M C K I — 120

AGTGGATTGGTCCAGGGAATATCTGTCGCCAGCTTCAGTCTTTTACGTTAGTTGCAATTGCTGTAGATAGGTTCCAGTGTGTGGTCTACCCTTTTAAACCAAAGCTCACTATCAAGACAGCG — 600
S G L V Q G I S V A A S V F T L V A I A V D R F Q C V V Y P F K P K L T I K T A — 160

TTTGTCATTATTATGATCATCTGGGTCCTAGCCATCACCATTATGTCTCCATCACCATTATGTCTCCAGCAGTAATGCTGCAACTACCGAGTGAGACTCCAGAATAAAACC — 720
F V I I M I W V L A I T I M S P S A V M L H V Q E E K Y Y R V R L N S Q N K T — 200

AGTCCAGTGTACTGGTGCCGGGAGACTGGCCAAATGAGGAAATCAGGAAGATCTACACCACCGTGCTGTTTGCCAACATCTACCTGGCTCCCCTCTCCCTCATTGTCATCATGTATGGA — 840
S P V Y W C R E D W P N Q E M R K I Y T T V L F A N I Y L A P L S L I V I M Y G — 240

AGGATTGGAATTTCACTCTTCAGGGCTGCAGTTCCTCACACAGGCAGGAAGAACCAGGAGCAGTGGCACGTGGTGTCCAGGAAGAAGCAGAAGATCATTAAGATGCTCCTGATTGTGGCC — 960
R I G I S L F R A A V P H T G R K N Q E Q W H V V S R K K Q K I I K M L L I V A — 280

CTTGCTTTTATTCTCTCATGGCTGCCCCCTGTGGACTCTAATGATGCTCTCAGACTACGCTGACCTTTCTCCAAATGAACTGCAGATCATCAACATCTACACTCCCTTTTGCACACTGG — 1080
L L F I L S W L P L W T L M M L S D Y A D L S P N E L Q I I N I Y Y P F A H W — 320

CTGGCATTCGGCAACAGCAGTGTCAATCCCATCATTTATGGTTTCTTCAACGAGAATTTCCGCCGTGGTTTCCAAGAAGCTTTCCAGCTCTGCCAAAAAGAGCAAAGCCTATG — 1200
L A F G N S S V N P I I Y G F F N E N F R R G F Q E A F Q L C Q K R A K P M — 360

GAAGCTTATACCCTAAAAGCTAAAAGCCATGTGCTCATAAACACATCTAATCAGCTTGTCCAGGAATCCACATTCAAAACCCTCATGGGGAAACCTTGCTTTATAGGAAAAGTGCTGAA — 1320
E A Y T L K A K S H V L I N T S N Q L V Q E S T F Q N P H G E T L L Y R K S A E — 400

AAACCCCAACAGGAATTAGTGATGGAAGAATTAAAAGAAACTACTAACAGCAGCTAGTGTGATAATCCTAACTCTACTACGCATTATATATTAAATCCATTGC — 1440
K P Q Q E L V M E E L K E T T N S S E I * — 421

TM1 47-69
TM2 82-104
TM3 121-141
TM4 160-182
TM5 218-240
TM6 275-297
TM7 312-336

Fig.2

Amino Acid Homologies of A4 and Related Mammalian Receptors

Note: All sequences are human
Numbers below represent % similarity / % identity

	A4	Orexin1	Orexin2	Y1	Y2	Y4	Y5	Gastrin	CCKA	NK1	Mu
A4	100	59/32	61/32	63/31	61/30	59/28	61/28	61/28	63/31	55/26	62/25
Orexin1		100	84/69	58/26	59/32	64/32	61/26	58/27	59/30	59/32	58/26
Orexin2			100	60/27	60/31	63/32	59/26	61/29	58/29	56/31	58/28
Y1				100	63/31	71/43	66/32	60/30	56/28	54/29	54/24
Y2					100	62/33	63/32	56/27	56/29	59/30	57/24
Y4						100	64/29	54/29	56/28	53/26	54/25
Y5							100	58/28	55/26	57/24	61/26
Gastrin								100	73/50	55/27	58/24
CCKA									100	57/30	55/26
NK1										100	60/26
Mu											100

Legend:

Code:	GenBank Assession No.	Description
Orexin1	AF041243	Human Orexin receptor-1
Orexin2	AF041245	Human Orexin receptor-2
Y1	P25929	Human Neuropeptide receptor Type1
Y2	P49146	Human Neuropeptide receptor Type2
Y4	P50391	Human Neuropeptide receptor Type4
Y5	U56079	Human Neuropeptide receptor Type5
Gastrin	P32239	Human Gastrin/Cholecytokinin Type B receptor
CCKA	P32238	Human Cholecystokinin Type A receptor
NK1	P25103	Human Neurokinin-1/Substance-P receptor
Mu	P35372	Human Mu-type opioid receptor

Fig.3

A4 vs. Human Y1 receptor

Percent Similarity: 63.032
Percent Identity: 30.585

```
  1 MNEKWDTNSSENWHPIWNV.NDTKHHLYSDINXTYVNYYLHQPQVAAIFI  49
      |.   :.:|  |:.  |   :|: |   .:.:   ::.::   :|
  1 .........MNSTLFSQVENHSVHSNFSEKNAQLLAFENDDCHLPLAMI  40

 50 ISXFL....IFFLCMMGNTVVCFIVMRNKHMHTVTNLFILNLAISDLLVG  95
      :.   |      ::.|.:  ||  .:.:|::::|:|:.|||::|:||::|||||:
 41 FTLALAYGAVIILGVSGNLALIIIILKQKEMRNVTNILIVNLSFSDLLVA  90

 96 IFCMPITLLDNIIAGWPFGNTMCKISGLVQGISVAASVFTLVAIAVDRFQ 145
      |:|:|:|::  .::. |.||::|||:...:||.:|::.|:|.|| |||:| |
 91 IMCLPFTFVYTLMDHWVFGEAMCKLNPFVQCVSITVSIFSLVLIAVERHQ 140

146 CVVYPFKPKLTIKTAFVIIMIIWVLAITIMSPSAVMLHVQEEKYYRVRLN 195
      :: |   :  . : |:| | :|||||:: | :  : :|.: .| |:
141 LIINPRGWRPNNRHAYVGIAVIWVLAVASSLPFLIYQVMTDEPFQNVTLD 190

196 SQNKTSPVYWCREDWPNQEMRKIYTTVLFANIYLAPLSLIVIMYGRIGIS 245
      : :..  | |  ::: |.:.  |   |||:|:.  |::||::|.| | :| |.
191 AYKDK...YVCFDQFPSDSHRLSYTTLLLVLQYFGPLCFIFICYFKIYIR 237

246 LFRAAVPHTGRKNQEQWHVVSRKKQKIIKMLLIVALLFILSWLPLWTLMM 295
      || .   :::.  |  |...::| |||  :.: | ::|||| .:
238 LKRRNNMMDKMRDNKYR...SSETKRINIMLLSIVVAFAVCWLPLTIFNT 284

296 LSDYADLSPNELQIINIY....IYPFAHWLAFGNSSVNPIIYGFFNENFR 341
      :  |:.:       |||..:    :: :.|:  |:  ..:||||:|||:|.||:
285 VFDWNH......QIIATCNHNLLFLLCHLTAMISTCVNPIFYGFLNKNFQ 328

342 RGFQEAFQLQLCQKRAKPMEAYTLKAKSHVLINTSNQLVQESTFQNPHGE 391
      |::|  |   | :::|: |::.  :.|.  |.| : .:.|:   ::    ::.
329 RDLQ..FFFNFCDFRSRD.DDYETIAMSTMHTDVSKTSLK.......QAS 368

392 TLLYRKSAEKPQQELVMEELKETTNSSEI* 421
      .:  ::|  .:::.::| :
369 PVAFKKINNNDDNEKI*........... 385
```

Fig.4

Amino Acid Comparison

Human A4 Receptor vs. Human Orexin Receptor-2

Percent Similarity:	60.500
Percent Identity:	31.500

Gap Weight:	30
Length Weight:	1

Top seqeunce:	Human Orexin receptor-2
Bottom Seqeunce:	Human A4 receptor

```
  1 MSGTKLEDSPPCRNWSSASELNETQEPFLNPTDYDDEEFLRYLWREYLHP 50
    |.:..   |. :: || : .::|:|::.:....:  .  ::     |||.
  1 MNEKW..DTNSSENWHPIWNVNDTKHHLYSDINXTYVNY.......YLHQ 41

 51 KEYEWVLIAGYIIVFVVALIGNVLVCVAVWKNHHMRTVTNYFIVNLSLAD 100
    .: . ::| : :::|..:.:||.:||. | :|.||:||||.||:||:::|
 42 PQVAAIFIISXFLIFFLCMMGNTVVCFIVMRNKHMHTVTNLFILNLAISD 91

101 VLVTITCLPATLVVDITETWFFGQSLCKVIPYLQTVSVSVSVLTLSCIAL 150
    :||:| |:| ||: :|..:| ||:.:||: ..:|::||:.||:|| .||:
 92 LLVGIFCMPITLLDNIIAGWPFGNTMCKISGLVQGISVAASVFTLVAIAV 141

151 DRWYAICHPLMFKSTAKRARNSIVIIWIVSCIIMIPQAIVME.....CST 195
    ||: .:..|:. | | | |  |:|||::::..|| | |:::::    :
142 DRFQCVVYPFKPKLTIKTAFVIIMIIWVLAITIMSPSAVMLHVQEEKYYR 191

196 VFPGLANKTTLFTVCDERWGGEIYPKMYHICFFLVTYMAPLCLMVLAYLQ 245
    |  : .|||.. | | |.:: .|:| ..:| .|:|||:|:|: | :
192 VRLNSQNKTSPVYWCREDWPNQEMRKIYTTVLFANIYLAPLSLIVIMYGR 241

246 IFRKLWCRQIPGTSSVVQRKWKPLQPVSQPRGPGQPTKSRMSAVAAEIKQ 295
    |  .|:  .:| |:.  | :|..:
242 IGISLFRAAVPHTGEKNQEQWHVV.......................... 265

296 IRARRKTARMLMVVLLVFAICYLPISILNVLKRVFGMFAHTEDRETVYAW 345
    |  :|. :||::| |:| :::||:..| :|.  :: ::. :  .:|
266 SRKKQKIIKMLLIVALLFILSWLPLWTLMMLSDYADLSPNELQIINIYI. 314

346 FTFSHWLVYANSAANPIIYNFLSGKFREEFKAAFSCCCLGVHHRQEDRLT 395
    :.|:|||.:||:.|||||||:|:.::|| :|:.||    |.: ::::...:.
315 YPFAHWLAFGNSSVNPIIYGFFNENFRRGFQEAFQ...LQLCQKRAKPME 361

396 RGRTSTESRKSLTT.....QISNFDN...........ISKLSEQVVLTSI 429
     .:.|:  :.|    | |.|:|         .|  :::|:..:
362 AYTLKAKSHVLINTSNQLVQESTFQNPHGETLLYRKSAEKPQQELVMEEL 411

430 STLPAANGAGPLQNW* 445
    .. ..:.:
412 KETTNSSEI*...... 421
```

A4 vs. Human CCK receptor

Fig.5

Percent Similarity: 63.514
Percent Identity: 31.081

```
  1 ..MNEKWDTNSSENWHPIWNVNDTKHHLYSDINXTYVNYYLHQPQV.... 44
    :  :.: .|:|        ||..  .: ||.  ::|:||:.
  1 MDVVDSLLVNGS........NITPPCELGLENETL..FCLDQPRPSKEW 39

 45 .AAIFIISXFLIFFLCMMGNTVVCFIVMRNKHMHTVTNLFILNLAISDLL 93
    :|: |:   |||:|:::|||:|. :::|||:|:||||:|:|.||:|||:
 40 QPAVQILLYSLIFLLSVLGNTLVITVLIRNKRMRTVTNIFLLSLAVSDLM 89

 94 VGIFCMPITLLDNIIAGWPFGNTMCKISGLVQGISVAASVFTLVAIAVDR 143
    :.:|||||:.|:.|:: :: ||.:|||..:.. |.||:.|.|.||||:::|
 90 LCLFCMPFNLIPNLLKDFIFGSAVCKTTTYFMGTSVSVSTFNLVAISLER 139

144 FQCVVYPFKPKL..TIKTAFVIIMIIWVLAITIMSPSAVMLHVQEEKYYR 191
    :..:. |:::::  |  .|: :|  .|.|::|||.| ::   ::
140 YGAICKPLQSRVWQTKSHALKVIAATWCLSFTIMTPYPIYSNL....... 182

192 VRLNSQNKTSPVYWCREDWPNQEMRKIYTTVLFANIYLAPLSLIVIMYGR 241
    |.:..:|: .: ||  :||: |:: : |.|: ::| | :::: ||
183 VPFTKNNNQTA.NMCRFLLPNDVMQQSWHTFLLLILFLIPGIVMMVAYGL 231

242 IGISLFRA....AVPHTGRKNQEQWHVVSRK.................. 268
    |::.|:::   | ...:.|::... .||
232 ISLELYQGIKFEASQKKSAKERKPSTTSSGKYEDSDGCYLQKTRPPRKLE 281

269 ..........................KQKIIKMLLIVALLFILSWLPLWT 292
                              |:::|:||:::.:||:|:|:|::.
282 LRQLSTGSSSRANRIRSNSSAANLMAKKRVIRMLIVIVVLFFLCWMPIFS 331

293 LMMLSDYADLSPNELQIINIYIYPFAHWLAFGNSSVNPIIYGFFNENFRR 342
    :..|.. |:: : :.  .:| :|:::.|:||||||.|:|..||
332 ANAWRAYDTASAE..RRLSGTPISFILLLSYTSSCVNPIIYCFMNKRFRL 379

343 GFQEAFQLQLCQKRAKPMEAYTLKAKSHVLINTSNQLVQESTFQNPHGET 392
    || .:|                ::. :: :.. :. :: :::| ..: :
380 GFMATF.............PCCPNPGPPGARGEVGEEEEGGTTGASLSRF 416

393 LLYRKSAEKPQQELVMEELKETTNSSEI* 421
    . :||. |.|
417 SYSHMSASVPPQ................ 428
```

Fig.6